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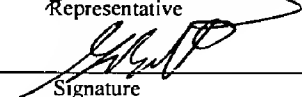
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Applicants : Nacamulli et al.
Serial No. : 09/099,048
Reissue of: : U.S. Patent No. 5,527,710
Filed : June 17, 1998
For : **RATE MEASUREMENTS OF BIOMOLECULAR
REACTANTS USING ELECTROCHEMILUMINESCENCE**
Group Art Unit : 1641
Examiner : M. E. Ceperley

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Gerard Bilotto Reg. No. 51,474
Name of Applicant, Assignee or Registered
Representative


Signature

September 26, 2002
Date of Signature

AMENDMENT UNDER PROVISION 37 C.F.R. § 116

Marked up version

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The response to the Final Official Action dated March 26, 2002 (the "Final Official
Action") was due on June 26, 2002. However, Applicants are hereby submitting a Petition For A

Three-Month's Extension Of Time. Therefore the due date is September 26, 2002 and hence this Amendment is timely filed. A Notice of Appeal is submitted herewith.

In response to the Final Official Action under provision 37 C.F.R. § 116 please amend the above-identified application as follows:

IN THE CLAIMS

37. (Thrice Amended) A method for determining the time course of a reaction in which at least one reactant is converted to one or more products, said method comprising:

- (a) forming a composition containing said reactant and a luminophore, wherein
 - (i) the reactant reacts to form a reaction product;
 - (ii) the luminophore is capable of being induced to emit an electrochemiluminescence signal, wherein electrochemiluminescence emitted by said luminophore is affected by said reaction; and
 - (iii) the electrochemiluminescence signal emitted upon exposure of said composition to electrical energy changes as the reaction progresses; and
- (b) exposing the composition to electrical energy at selected time intervals and measuring the electrochemiluminescence signal during said selected time intervals [to determine the time course of the reaction]; and
- (c) [calculating the time course of the reaction from] relating the ECL signals measured in step (b) to the concentration of said reactant or said product to determine the time course of said reaction.

76. (Twice amended) A method for determining the time course of a reaction in a composition containing a luminophore wherein said composition is exposed to electrical

energy at selected time intervals during said reaction to induce said luminophore to emit an electrochemiluminescent signal under conditions which relate the concentration of a reactant or a product of the reaction to the intensity of said electrochemiluminescent signal and said electrochemiluminescent signal is measured during said selected time intervals to determine said time course of reaction.

Please add the following new claims:

- 94. (New) A method for determining the time course of a reaction in which at least one reactant is converted to a product comprising:
- (a) forming a composition containing said reactant, a reaction partner and a luminophore, wherein:
 - (i) said reactant reacts with said binding partner to form said product; and
 - (ii) the luminophore is capable of being induced to emit an electrochemiluminescence signal;
 - (b) exposing said composition to a series of a pre-selected potential voltage pulses of pre-selected duration at pre-selected intervals of time to produce a modulated electrochemiluminescence signal, wherein said electrochemiluminescence signal is produced under reaction conditions which relate the concentration of said reactant or said product to the intensity of said electrochemiluminescence signal;
 - (c) measuring said modulated electrochemiluminescence signal; and
 - (d) determining the time course of said reaction by demodulating said modulated electrochemiluminescence signal.

95. (New) A method for determining the time course of a binding reaction of a reactant and a binding partner comprising:

- (a) forming a composition containing said reactant, said binding partner and a luminophore, wherein:
 - (i) said reactant binds said binding partner to form a complex; and
 - (ii) said luminophore is capable of being induced to emit an electrochemiluminescence signal;
- (b) exposing said composition to a series of pre-selected potential voltage pulses of pre-selected duration at pre-selected intervals of time to produce a modulated electrochemiluminescence signal, wherein said electrochemiluminescence signal is produced under reaction conditions which relate the concentration of said reactant or said complex to the intensity of said electrochemiluminescence signal;
- (c) measuring said electrochemiluminescence signal; and
- (d) determining the time course of said binding reaction by demodulating said modulated electrochemiluminescence signal.

96. (New) A method for determining the time course of an enzymatic reaction comprising:

- (a) forming a composition containing an enzyme, enzyme substrate and a luminophore, wherein:
 - (i) said enzyme converts said substrate to a reaction product;

- (ii) said luminophore is capable of being induced to emit an electrochemiluminescence signal;
- (b) exposing said composition to a series of pre-selected potential voltage pulses of pre-selected duration at pre-selected intervals of time to produce a modulated electrochemiluminescence signal, wherein said electrochemiluminescence signal is produced under reaction conditions which relate the concentration of said substrate or said product to the intensity of said electrochemiluminescence signal;
- (c) measuring said electrochemiluminescence signal; and
- (d) determining the time course of said enzymatic reaction by demodulating said electrochemiluminescence signal. --

REMARKS

Favorable reconsideration and allowance of the above-identified application is respectfully requested in view of the amendments and remarks herein.

Claims 1-51, 53-56 and 76-93 are pending in this application. Claims 1-36 are allowed.

The Examiner has rejected claims 37-51, 53-56 and 76-93 as follows:

- 1) Claims 37-51, 53-56 and 76-93 are rejected under 35 U.S.C. 112, first paragraph, written description requirement;
- 2) Claims 37-51, 53-56 and 76-93 are rejected under 35 U.S.C. 112, second paragraph as allegedly "being confusing, indefinite and/or incomplete"; and
- 3) Claims 37-51 and 53-93 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over each of (1) Martin et al, Bard et al or Shibue et al taken in combination with each of (2) Karlsson et al, Sieber or Freundlich et al.

Claims 37 and 76 have been amended and new claims 94-96 have been added to more particularly point out and distinctly define the invention. The claims are fully supported in the disclosure of U.S. 5,527,710 (the '710 patent) and are fully enabled. No new matter has been added.

1. **Claims 37-51, 53-56 And 76-93 Are Fully Supported In The Specification**

Claims 37-51, 53-56 and 76-93 are rejected under 35 U.S.C. 112, first paragraph, as allegedly "not corresponding with the enabling written description of the invention" (Final Official Action, p. 2, par. 4) and for the reasons "stated in paragraphs 5 and 6 of the August 14, 2000 Official action and maintained in paragraphs 3 and 6 of the April 25, 2001 Official Action" (Final Official Action, p. 3, par. 6).

a). With respect to claims 37-51 and 53-56, the Examiner alleges that in paragraph 4(a), p. 2 of the Final Official Action that "There appears to be no description in the originally filed specification of either the 'one or more products' and their exact composition or what is involved in the 'calculating' step".

Applicants respectfully traverse. A person of ordinary skill in the art would readily understand that the 'calculating' steps according to the instant invention means relating the ECL intensity back to the concentration of reactant or product. The specification clearly defines what constitutes the 'calculating' steps according to the instant invention: "A biomolecular reaction which is monitored according to the present invention must be carried out using a luminophore under reaction conditions which relate the concentration of a reactant or a product of the reaction to the ECL intensity." (Specification, col. 2, lines 22-26).

However, to further prosecution of the application, claim 37 has been amended and does not recite "calculating" steps. Claims 38-51 and 53-56 are dependent on claim 37. Also newly

added claims 94-96 conform to the Examiner's suggestions and do not recite the "calculating" steps. Accordingly, Applicants respectfully request that this aspect of the rejection be withdrawn for claims 37-51 and 53-56.

With respect to the Examiner's objection to the term "one or more products", The invention relates to the measurement of a time course of a reaction. A reaction by definition transforms reactants into products. The reactions of the invention can generate one product (e.g., the reaction of an antibody with an antigen to form a binding complex as in Example 5) or can generate more than one product (See, e.g., the scheme in Example 1). Therefore the meaning of "one or more products" would be easily recognized by a person of ordinary skill in the art in view of the disclosure in the specification. Although Applicants do not agree with this objection, newly added claims 95 and 96 specifically claim binding and enzymatic reactions and do not recite "one or more products".

b). With respect to claims 76-93, the Examiner alleges in paragraph 4(b), p. 2 of the Final Official Action that "There appears to be no description in the originally filed specification to support the method of newly presented claim 76". The Examiner further alleges that "in the absence of the recitation of any reactants, the method of claim 76 would encompass a method of measuring the time course of electrochemiluminescence decay of the luminophore per se...." (Final Official Action, p. 2, par. 4(b)).

Applicants respectfully submit that claim 76 fully complies with the first paragraph of 35 U.S.C. 112 for the reasons set forward in Applicant's previous responses. However, to further the prosecution of the application, Claim 76 has been amended to further define the instant invention. Claims 77-93 are dependent on claim 76. Every limitation of claim 76 is clearly described in the specification.

The specification clearly states:

A biomolecular reaction which is to be monitored according to the present invention must be carried out using a luminophore under reaction conditions which will relate the concentration of a reactant or a product of the reaction to the ECL intensity.

[Specification, col. 2, lines 22-26; see also each of Examples 1-5].

The specification further describes how this monitoring is carried out so as to follow a reaction in progress:

The biomolecular reaction is carried out in an electrochemical cell and a series of electrical pulses are applied at a preselected potential and at preselected constant intervals of time and constant duration to modulate the ECL output. The intensity of the resulting luminescence is measured at the same intervals to provide a timed series of values called reaction in progress (P).

[Specification, col. 2, lines 36-42]

Therefore one of ordinary skill in the art would recognize that the invention is broadly related to measurements of luminescence intensity under conditions which will relate the luminescence intensity to the concentration of a reactant or a product and that Applicants had possession of the claimed invention at the time of filing the application. Applicants maintain that the “written description” rejection is improper and should be withdrawn. Applicants remind the examiner that the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) for the disclosure to satisfy the description requirement (MPEP 2163.02). The Examiner has the initial burden of establishing why a person of ordinary skill in the art would not recognize in an applicant’s disclosure a description of the invention as defined by the claims (MPEP 2163.04). If the Examiner determines that any limitations of the dependent claims 77-93 are not supported in the specification, the Examiner is specifically invited to identify such limitations so the Applicants will have an opportunity to respond.

With respect to the Examiner's allegations that "in the absence of the recitation of any reactants, the method of claim 76 would encompass a method of measuring the time course of electrochemiluminescence decay of the luminophore per se...[which is not supported by] the originally filed specification." One of ordinary skill in the art would understand from the description in the specification that the luminophore is used as an indicator to relate the concentration of a reactant or product (See, Specification, col. 2, lines 22-26 and Claim 76). Claim 76 has been amended to more clearly state this relationship between the luminophore and the reactant or product.

Thus, Applicants urge that the claims are fully supported by the specification as originally filed in compliance with the first paragraph of 35 U.S.C. 112. Therefore, the rejection of claims 37-51, 53-56 and 76-93 under 35 U.S.C. 112, first paragraph, is improper and should be withdrawn.

c). In response to the Examiner's rejection of claims 37-51 and 53-93 in paragraphs 6(a) and 6(b), p. 2 of the Final Official Action, Applicants submit that claims 37-51 and 53-93 fully comply with the first paragraph of 35 U.S.C. 112.

The specification broadly describes methods of measuring the rate of reactions using electrochemiluminescence. There is no reasonable basis to allege that one of ordinary skill in the art would not recognize that applicants had possession of the claimed invention at the time of filing. Contrary to the Examiner's statement (Final Official Action, p. 3, par. 6(a)) that Applicants are selectively ignoring certain recitations in the specification, it appears that the Examiner is misinterpreting such recitations. The Examiner specifically refers to the following recitation "the reagents employed in the reaction, therefore **will include a reaction partner** which reacts with the **reactant...**" (Specification, col. 2, lines 27-28). Apparently the Examiner

is interpreting this recitation as follows: “the reagents employed in the reaction, therefore must include a reaction partner which reacts with the reactant...” This assumption is not warranted by the instant specification. For example, reactions such as autocleavage of a serine protease or autophosphorylation of EGFR (epithelial growth factor receptor) do not involve a reaction partner. Similarly the instant invention does not necessarily involve a reaction partner.

Moreover, with respect to the examiner's statement regarding the requirement for modulation and demodulation, the specification states that the methods of the invention are “carried out using a luminophore under reaction conditions which will relate the concentration of a reactant or a product of the reaction to the ECL intensity”. There is no reasonable basis to assert that this “calculation” should be limited to the one specific set of modulation and demodulation steps described in the application.

However, to further the prosecution of the application, new claims 94-96 have been added that include a reaction partner, modulation and demodulation steps, as suggested by the Examiner. The amendment is believed to alleviate the basis of this rejection.

Accordingly, Applicants maintain that the claims 37-51, 53-56 and 76-93 are fully supported by the specification as originally filed for the reasons set forth above and in the Applicant's previous reply. Favorable reconsideration and withdraw of the rejection are respectfully requested.

**2. Claims 37-51, 53-56 And
76-93 Are Not Indefinite**

The Examiner rejects claims 37-51, 53-56 and 76-93 under 35 U.S.C. 112, second paragraph as allegedly “being confusing, indefinite and/or incomplete” (Final Official Action, p. 3, par. 5) and for the reasons set forth in paragraph 8 of the August 14, 2000 Official Action (Final Official Action, p. 4, par. 7). More specifically, the Examiner objects to the terms “one or

more products” and “calculating” step in claim 37 and for allegedly “failing to define the ‘reaction’ to be measured” in claim 76.

a). With respect to the Examiner’s objections to claim 37 for the use of the terms “one or more products” and “calculating” step, Applicants urge the claims are sufficiently clear and definite to one of ordinary skill in the art when properly construed in view of the specification and what is known in the art (see the discussion of these terms under section 1 above). Accordingly, Applicants request that the rejection of the claims 37-51, 53-56 and 76-93 be withdrawn.

In addition, to further the prosecution of the application new claims 94-96 have been added which Applicants believe directly address and eliminate the Examiner’s stated objections.

b). With respect to the Examiner’s statement on p.3, par. 5(b) of the Final Official Action alleging Applicants “failing to define the ‘reaction’ to be measured” in claim 76, Applicants submit that amended claim 76 is sufficiently clear and definite in compliance with 35 U.S.C. 112, second paragraph. One of ordinary skill in the art would readily understand the meaning of the term “reaction” as used in the claim when properly construed in view of the specification. Claim 76 is directed to a general method for determining a reaction rate, which is applicable for a wide range of reactions. Examples of reactions which are specifically described in the Specification include: (i) NADH generation by Glucose-6-phosphate dehydrogenase (Example 1), (ii) NADH consumption by Lactate dehydrogenase, (iii) Streptavidin-Biotinylated DNA complex formation (Example 4) and (iv) CEA Antibody-Antigen binding (Example 5). There is no reasonable basis to assert that the claims need to be limited to the specific reactions described in the specification to comply with the second paragraph of 35 U.S.C. 112. Furthermore, the

Examiner is reminded that the MPEP specifically states that claim breadth should not be confused with indefiniteness:

Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

[MPEP 2173.04]

Accordingly, Applicants request that the rejection of claims 37-51, 53-56 and 76-93 under 35 U.S.C. 112, second paragraph be withdrawn.

c). On p. 4, par. 7, lines 12-15 of the Final Official Action, the Examiner states that “although the examiner agrees with applicant’s statements that the claims must be read in light of the specification, the examiner and applicants do not agree what the enabling written description of the specification establishes as the ‘invention’”.

Applicants respectfully traverse. The MPEP clearly states:

The content of applicant’s specification is not used as evidence that the scope of the claims is inconsistent with the subject matter which applicants regard as their invention. As noted in *In re Ehrreich*, 590 F.2d 902, 200 USPQ 504 (CCPA 1979), agreement, or lack thereof, between the claims and the specification is properly considered only with respect to 35 U.S.C. 112, first paragraph; it is irrelevant to compliance with the second paragraph of that section.

[MPEP 2172]

Applicants urge that the scope of the protection sought is clearly defined and all of the claim limitations are sufficiently clear to a person of ordinary skill in the art. As cited above, the breadth of the claims is not to be confused with indefiniteness.

Therefore, the rejection is improper and should be withdrawn.

3. **Claims 37-51 And 53-93 Are Not Obvious**

The Examiner maintains the rejection of claims 37-51 and 53-93 under 35 U.S.C. 103(a) as allegedly being obvious over each of (1) Martin et al, Bard et al or Shibue et al taken in combination with each of (2) Karlsson et al, Sieber or Freundlich et al. (Final Official Action, p. 4, par. 8)

Applicants respectfully traverse. The presently claimed subject matter is not rendered obvious because none of the above cited references teach or suggest the feasibility of making the specific combination of the invention as suggested by the Examiner. That is, a combination consisting of multiple time series measurements (e.g. repeated sequential measurements at various time intervals) in the same solution without obtaining erroneous measurements. The test for patentability under 35 U.S.C. 103 is known as the "Graham factual inquiry" and the Examiner has the initial burden of proof to show obviousness. The Examiner has failed to do so. The MPEP states that:

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

- (A) The claimed invention must be considered as a whole;
 - (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
 - (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
 - (D) Reasonable expectation of success is the standard with which obviousness is determined.
- Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

[MPEP 2141]

With respect to Graham Tenet (A), Applicants submit that none of the references, alone or in combination, teach or suggest the instant invention as a whole. Applicants respectfully

submit that the Examiner does not provide the required factual support to establish a *prima facie* case of obviousness. The MPEP states that:

To establish *prima facie* obviousness of a claimed invention, **all the claim limitations must be taught or suggested by the prior art.** *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

[See MPEP 2143.03, emphasis added]

More specifically, the instant invention is directed to carrying out ECL measurements of reaction rates by exposing the reaction mixture to repeated ECL measurements at selected time intervals (See, e.g., Claims 37, 57, 62 and 76), i.e., by the application of a series of electrical pulses (See, e.g., Claims 51 and 53 and new claims 94-96). This is an important and non-obvious advancement in the fields of ECL. None of the references cited by the Examiner alone or in combination have addressed this possibility. The instant invention is not obvious over references that teach a single ECL measurement or references that teach applying an analytical procedure that does not involve repetitive excitation of luminophores by the application of voltage pulses. Therefore, Applicants maintain that the references cited by the Examiner alone or in combination do not teach the instant invention as a whole. The MPEP states that:

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

The court held “due to the admitted unobviousness of the first two steps of the claimed combination of steps, the subject matter as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made.” 535 F.2d at 69, 190 USPQ at 17 (emphasis in original).

[MPEP 2141.02]

With respect to Graham Tenet (B), Applicants maintain that none of the references teach or suggest the combination made by the Examiner.

The Examiner fails to address the fact that there is no suggestion to combine the cited references in the disclosures of Martin, Bard, or Shibue. As set forth in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000), it is improper to make a rejection based on the combination of references absent some motivation, suggestion or teaching of the desirability of making the specific combination:

Most of all inventions arise from a combination of old elements. ... Thus, every element of a claimed invention may often be found in the prior art. ... However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. ... Rather, **to establish obviousness based on combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.**

[Citation omitted, emphasis added]

Applicants urge that none of the references cited by the Examiner teach that ECL reactions can be performed repetitively in the same solution to determine the rate of a reaction. There is no motivation or suggestion in the cited references which would have motivated one of ordinary skill in the art to modify the teaches of Martin, Bard or Shibue in view of teachings of Karlsson et al, Sieber or Freundlich et al. In fact, in view of the potentially destructive chemical events discussed below (See Graham Tenet (D)), one of ordinary skill in the art would not have been motivated to combine the references as suggested by the Examiner. The suggestion to combine the elements must come from the cited references and not from the applicant's disclosure. The Examiner's statement that "In view of the fact that monitoring the time course of antigen-antibody and enzyme-enzyme substrate interactions using conventional techniques is well known in the art [...], it would be obvious to use the well known, equivalent ECL analytical techniques of reference (1) for the same purpose, as claimed" (Official Action, dated April 25,

2001, p. 6, par. 8) is insufficient to establish a prima facie case of obviousness. The Examiner is invited to distinctly point out where one of ordinary skill in the art can find a suggestion, or motivation to combine the cited references.

Applicants respectfully submit that the Examiner arrives at the conclusion of alleged obviousness using impermissible hindsight afforded by the instant invention (Graham Tenet (C)).

With respect to Graham Tenet (D), the disclosures of the cited references would not have provided one of ordinary skill in the art with a reasonable expectation of success with respect to the claimed methods of reaction rate measurement using electrochemiluminescence. One of ordinary skill in the art would not have been provided with a reasonable expectation of success from the cited references for carrying out such measurements, due to interference and/or destructive chemical events. (See MPEP 2143.02). The applicants would also like to direct the Examiner's attention to Chapter 29 on Dynamic Electrochemistry from a textbook of P. Atkins, *Physical Chemistry*, Freeman & Co. (1994), paragraphs 29.4 on Electrolysis and 29.7 on Corrosion. Based on the teaching of Atkins, a skilled artisan would expect electrode corrosion and solution electrolysis caused by the application of periodic electric pulses at preselected time intervals to interfere with the measurements of emitted light.

In addition the specification clearly describes that the prior art ECL measurements produced peak-shaped ECL signals (e.g. "The ECL then is observed as a sharp peak that decays with time", specification col. 4, lines 60-61) The peak shape of the ECL emission was accepted in the prior art as indicative of the destructive nature of the ECL measurement and an indication that it is not suitable for kinetic measurements. The instant invention describes an unobvious improvement wherein by applying an electrical potential in controlled pulses, the destructive effect of ECL could be slowed while retaining the ability to conduct kinetic measurements.

(Specification, col. 4, line 48 -- col. 5, line 36). Neither of the references alone or in combination, teach or suggest this limitation of the present invention and therefore they do not teach this invention as a whole.

The Examiner does not provide the required factual support to establish that a person of ordinary skill in the art would have a reasonable expectation of success for carrying out repetitive ECL measurements in a single solution. Therefore, the Final Official Action fails to provide the initial burden of proof required for establishing a prima facie case of obviousness.

Applicants maintain that the instant invention is not obvious over each of (1) Martin, Bard or Shibue, alone or in combination with each of (2) Karlsson, Sieber or Freundlich in view of the arguments set forth above and set forth in the previous response to the Official action dated April 25, 2001. Favorable reconsideration and withdrawal of the Section 103 rejection are earnestly solicited.

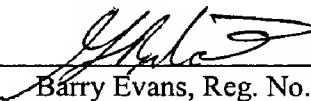
4. The original patent, or an affidavit or declaration as to the loss or inaccessibility of the original patent, will be submitted before this reissue application is allowed. Therefore the Examiner is asked to hold this issue in abeyance until the claims are allowable.

In view of the comments herein, the present application is believed to be in condition for allowance or in better condition for an appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Moreover, due to the large number of issues present in this Final Official Action, Applicants believe that an interview would be helpful in addressing any further issues or concerns, which the Examiner may have. Thus, Applicants respectfully request an interview with the Examiner once this Response has been reviewed.

Respectfully submitted,

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